REMARKS/ARGUMENTS

Claims 3-6 are pending in this application. All of these claims are rejected. In this response, claims 5 and 6 are cancelled without prejudice or disclaimer. Following the entry of this response, only claims 3 and 4 will remain pending in the application. Reconsideration of the application is respectfully requested.

Claim Rejections Under 35 U.S.C. 112

Claims 3 and 5 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. The Examiner notes the phrase; "neurodegenerative phase of multiple sclerosis" in the subject claims and alleges that one of ordinary skill would not be able to ascertain which part of multiple sclerosis is the "neurodegenerative phase" of the disease. The cancellation (without prejudice or disclaimer) noted above of claim 5 renders the rejection moot as to that claim. The rejection is, however, respectfully traversed insofar as it is directed to claim 3.

Applicants submit in response to the rejection that one having an ordinary level of skill at the time the presently claimed drug preparation method would, indeed, recognize the meaning of the phrase, " the neurodegenerative phase of multiple sclerosis", i.e., which is contrasted (see below) with the "inflammatory phase" of the disease. As evidence that the meaning of the term would be well understood by those working in this field of art, applicants cite to the paper by Steinman et al., Multiple Sclerosis: Deeper Understanding of its Pathogenesis Reveals New Targets For Therapy, *Annu. Rev. Neurosci.* (2002), 25: 491-505, which was cited on Form PTO-892 by the Examiner in the present Office Action. The Examiner's attention is respectfully directed therein to p. 502, second paragraph and Fig. 1, which demonstrate conclusively that, "neurodegenerative phase of multiple sclerosis" is indeed a 'term of art' that is well understood by those working in this field.

Further to the above, and as additional evidence that the indicated terminology is well understood by those having ordinary skill in this area, enclosed with this Response is a copy of another paper by Dr. Steinman, i.e., Steinman, Multiple sclerosis; a two-stage disease, *Nature Immunology* (2001), 2: 762-764. The reference clearly discusses the two states of multiple sclerosis, i.e., (a) autoimmune attack and (b) neurodegeneration, wherein the latter is commonly referred to as the "neurodegenerative phase" of the disease.

The new Steinman reference is listed on the form attached hereto and the Examiner is respectfully requested to review it and make it of record in the present application.Credit card payment in the amount of $180.00 for the required fee is being submitted herewith via EFS-Web.

Since, as demonstrated above the terminology at issue has been demonstrated as being clear and well understood by those working in this field, the Examiner is respectfully requested to reconsider and withdraw the rejection of applicants' claims under 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §102

Claims 5 and 6, which are directed to a pharmaceutical composition, are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Smith, et al., The P2X7 purinergic receptor on bovine macrophages mediates mycobacterial death, *Veterinary Immunology and Immunopathology*, (2001) 78: 249-262, for the reasons set forth on pp. 3-4 of the Office Action.

Claims 5 and 6 of the application have, however, been cancelled, as noted above, without prejudice or disclaimer, from this application. The 'anticipation' rejection is thus rendered moot and should therefore be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Claims 3 and 4, directed to a method for preparing a drug for treatment of the neurodegenerative phase of multiple sclerosis in mammals, is rejected under 35 U.S.C. §103 over Smith et al. (see above) and Neely (WO 99/38532) and in view of Jameson et al. (USP 5,589,458) and further in view of Steinman et al., Multiple Sclerosis: Deeper Understanding of its Pathogenesis Reveals New Targets for Therapy, *Annu. Rev. Neurosci.* (2002) 25: 491-505 for the reasons set forth on pp. 5-7 of the Office Action. The rejection is respectfully traversed.

In response to the rejection, applicants submit that Smith et al. discloses that P2X7 is an ionotropic channel regulated by ATP, playing an important role in a variety of immune responses (see p. 249 in the Introduction) and an important effector pathway of immune response (see p. 260, first paragraph). The reference mentions, further, that o-ATP and KN-62 are antagonists of the purinergic receptors P2X7 (see p. 260 first paragraph). The reference, however, does not contain any mention regarding the treatment of, specifically, the neurodegenerative phase of

multiple sclerosis, i.e., as recited in applicants' claim 3 and claim 4 as well, i.e., due to its dependency on the independent claim, claim 4.

The Neely reference (WO 99/38532) discloses a method for inhibiting fibrosis and sclerosis in a subject with a sclerotic disorder by administration of an amount of a P2X antagonist (see p. 4, lines 14-17). The reference also discloses that sclerosis is a loss of muscular function due to an increase in fibrosis.

The Jameson et al. '458 U.S. patent discloses that autoimmune diseases are characterized by an immune reaction against the subject's own antigens. Autoimmune diseases include lupus eritematous (SLE), rheumatoid arthritis (RA) and Multiple Sclerosis (MS).

Turning to the Steinman, et al. reference, applicants submit that the reference discloses that MS usually begins in adulthood with an autoimmune inflammatory attack against the myelin components. Paralysis, sensory disturbance in coordination and visual impairment are common characteristics of MS. The disease normally starts with attacks lasting from days to weeks, followed by remission lasting from months to years. Usually, these phases of remission last for 5 to 10 years.

Further according to the reference, about 30% of individuals with relapsing-remitting MS enter into a secondary chronic progressive state. In the chronic state, distinct attacks are rare and the disease progresses insidiously. In rare cases, clinical disability starts with this progressive phase and in these cases the disease is referred to as primary progressive MS (see p. 491, second paragraph – p. 492, first paragraph).

The Office Action mentions that Steinman, et al. discloses that the use of neuroprotective agents blocking glutamate receptor subtypes has been a prime direction in the development of new therapies for neurodegenerative conditions and may prove useful for the chronic degenerative phase of MS. The reference additionally mentions that the recognition of an inflammatory and neurodegenerative phase of MS has allowed the targeting of therapies specific for various phases of MS (see p. 502 second paragraph).

The Examiner thus considers, based on the combined disclosure of the cited references, that it would have been 'obvious' for one of ordinary skill in this art at the time the claimed preparation method was developed, to treat an autoimmune disease such as MS in the manner taught by applicants. As the applicants understand the reasoning being applied by the Examiner in support of this rejection, the Examiner is arguing that a skilled artisan would have been

motivated to treat an autoimmune disease, e.g., MS, since o-ATP is an important immune response effector as mentioned in Smith, et al. and antagonists, i.e., P2X are useful in the treatment of fibrosis and sclerosis according to the Neely reference. The Examiner, moreover, then adds that it is known that the recognition of an inflammatory and neurodegenerative phase of MS has allowed the targeting of therapies specific for various phases of MS, i.e., which is an autoimmune disease according to Jameson '458 and Steinman, et al. Thus, as indicated above, the Examiner concludes from the combined disclosures of the cited references, as summarized above, that one having an ordinary level of skill in the relevant art would have had a reasonable expectation of success in developing the claimed method of preparation.

It appears to the applicants, however, that the reasoning applied to reject the claims is self-contradictory. On the one hand the Office Action indicates that Multiple Sclerosis is an autoimmune disease, and also that o-ATP, a known P2X7 antagonist, is an important effector of an immune response. On the other hand, however, the Examiner appears to acknowledge that MS has two phases, i.e., an inflammatory phase – based on the autoimmune attack, and a neurodegenerative phase – based on the toxicity induced by the presence of metabolites and/or neurotransmitters, such as glutamate as mentioned in Steinman, et al. Applicants believe that the contradiction noted above is contained in the Examiner's holding that one having at least an ordinary level of skill in this field would be motivated to use P2X7 antagonists to treat MS due to its aspect as an autoimmune disease.

The present application demonstrates that the P2X7 receptors are present in oligodendrocytes and that by blocking these receptors with antagonists, such as o-ATP, their survival is achieved in a model of MS. Based on this, the use of P2X7 antagonists is demonstrably effective for treating the neurodegenerative phase of MS. The antagonists do not act toward the immune system by reducing the autoimmune inflammatory action produced during the inflammatory phase of the disease. On the contrary, however, they act by protecting against toxicity induced by ATP during the neurodegenerative phase of Multiple Sclerosis.

The above was not known, or even suggested at the time the process recited in claims 3-4 was developed by any of the cited references, taken individually or in the combination postulated by the Examiner. One having ordinary skill in this field of art would not, therefore, have been motivated to treat the neurodegenerative phase of MS with P2X7 antagonists because, firstly, it was not known at the time applicants' claimed method was developed that oligodendrocytes had

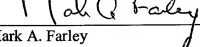
P2X7 receptors in their surface and, secondly, it was not known that the blocking of the channels increased the survival of oligodendrocytes in the neurodegenerative phase of MS.

Based on the reasons above, therefore, applicants submit that the claimed method for preparing a drug for the treatment of the neurodegenerative phase of multiple sclerosis in mammals was not, and should not be considered obvious, based on the cited combination of references relied upon by the Examiner. The Examiner is respectfully requested, therefore, to reconsider and withdraw the rejection of applicants' claims 3-4 under 35 U.S.C. §103.

THIS CORRESPONDENCE IS BEING SUBMITTED ELECTRONICALLY THROUGH THE PATENT AND TRADEMARK OFFICE EFS FILING SYSTEM ON November 16, 2010.

MAF: ck

Respectfully submitted,



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